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Trichloroacetic Acid Mediated Solvent-free Synthesis of Bis(indolyl)methanes Utilizing Grinding Technique

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ABSTRACT

An efficient, solvent free, one pot, synthesis of bis (indolyl) methane using indole and substituted aromatic aldehyde is achieved, through grinding technique at room temperature, in a short period of time giving the product in quantitative yield.

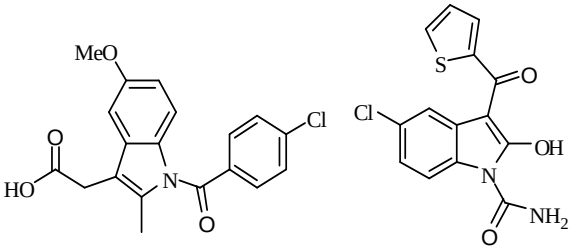
Keywords: Trichloroacetic acid, bisindolylmethanes, grinding technique, solvent free.

INTRODUCTION

Today with the growing epidome of environmental pollution worldwide, researchers are more concerned to use environmental benign reactions and techniques to perform organic transformation that can generate minimum amount of toxic waste material[1]. In a routine generality an organic synthesis is always performed in solvent system, which can bring the reactants in the reaction to interact fastly, solvate the reactant and through various interactive forces yields the product easily. But in an idea to generate environment friendly reactions, basically scientists thought to carry out reactions under solvent free condition, with a utility of simplified experimental procedure, without need of any special instrument or apparatus, lower the handling cost, easy work up procedure, atom economy, minimum energy and time consumption and greater reaction feasibility giving the sufficiently pure product in quantative yield by simple recrystallization only in some cases. Thus, a solvent-free organic synthesis or transformation is performed utilizing a reactant with irradiation under UV, ultrasonic, microwave, under thermal condition or sometimes solid acid catalysts like alumina, silica, clays, zeolites etc. Thus

with the growing importance of heterocyclic systems of pharmaceutical importance, solvent free synthesis is gaining importance in current era[2, 3].

Among the hetereocycles known indoles and their derivatives possess unique position in pharmaceutical[4], agrochemical[5] and material science[6],



Indomethacin **Tenidap**

Fig:01

which not only shows various physiological properties but also possess novel pharmacological activities[7]. Again it was well documented in the literature that, The hallucinogenic *bis*(indolyl) alkanes and their derivatives were first isolated from a fungus[8].

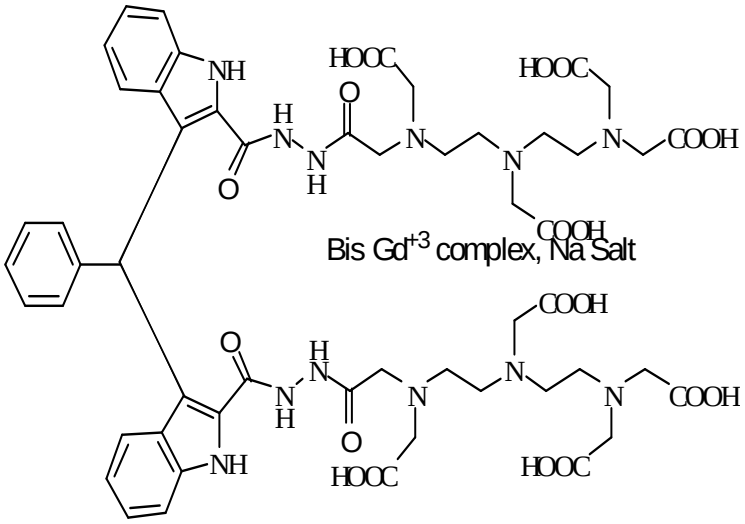


Fig 02: BIM complex (**B**)

Further a number of *bis*(indolyl)methanes or *bis* (indolyl)ethanes have been also isolated from marine sources[9]. *Bis*(indolyl)methanes was found in cruciferous plants are shown to promote beneficial estrogen metabolism in humans[10], act as an anticancer agent by inducing apoptosis in human[11a-c] cancer cells (breast cancer) and can act as highly selective fluorescent molecular sensors for Cu^{+2} ions[11d]. Indole derivatives like di (1-*H*-indolyl-3-yl) methanes (DIM) and 1, 4-*bis* [di (1*H*-indol-3-yl) methyl] benzenes are found to be useful in the treatment of fibromyalgia, chronic fatigue and irritable bowel syndrome[12]. Further these *bis*(indolyl)alkanes and their derivatives are shown to normalize abnormal cell growth associated with cervical dysplasia[13]. Thus these indole and 3-substituted indoles derivatives are shown to exhibit diverse pharmaceutical and therapeutic applications in drug discovery including, antiviral[14], antibiotics[15], cytotoxic[16], antioxidative[17], radical scavengers[18], antimicrobial[19] and insecticidal activities[17]. Further it was observed that, indole derivatives such as Indomethacin and Tenidap[20ab] (Fig 01) possess antiinflamatory activity alongwith

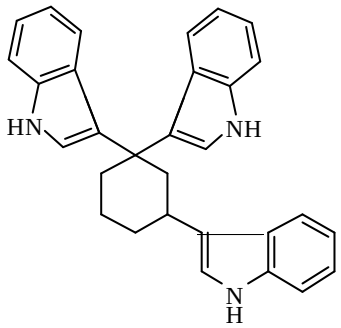


Fig 04: 1,1,3-Tris(3-indolyl)cyclohexane **(D)**

analgesic and antipyretic activities. BIMs forms complexes with Gd^{+3} *i.e.* B[20f] (Fig 02) which are useful as a contrast agents for radio-imaging and visualization of various tissues and organs. While 3, 3^1-bisindolyl-4-azaphthalides[20c,d,e] A (Fig 03) is used as color formers in pressure and heat-sensitive recording materials, *Bis*(5-methoxyindol-3-yl) methane[20g,h,I,j] C (Fig 03) acts as a chemotherapeutic against tumors, suppressing the growth of cancer cell

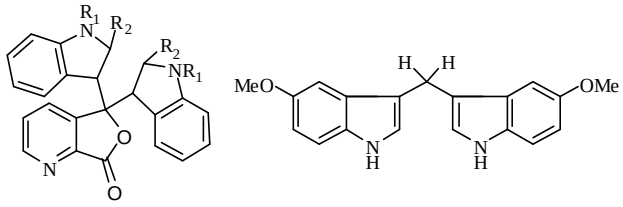
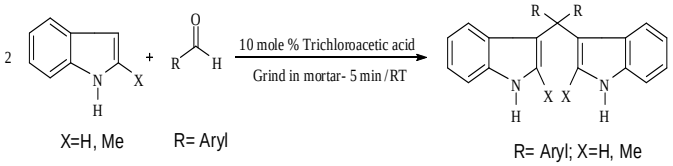


Fig 03: 3,3^1-bisindolyl-4-azaphthalides(**A**) & Bis(5-methoxyindol-3-yl) methane (**C**)

lines such as lungs (HOP-92), renal (A498) and breast (MDAMB-231/1TCC). Further it is observed that 1, 1, 3-tri (3-indolyl) cyclohexane[20k], D (Fig 04), reduces growth of lung cancer cells of xennograft models.

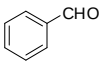
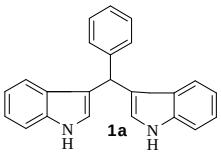
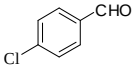
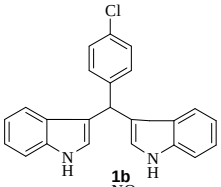
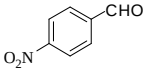
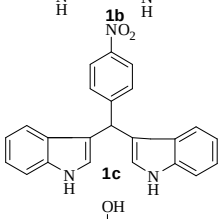
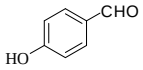
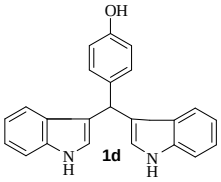
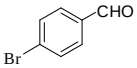
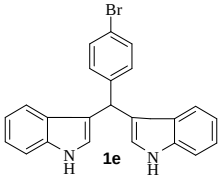
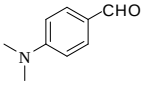
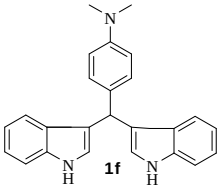
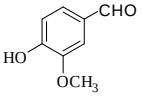
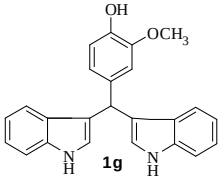


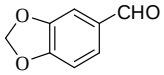
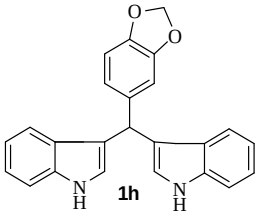
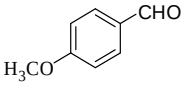
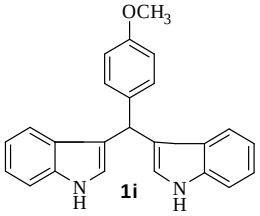
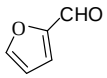
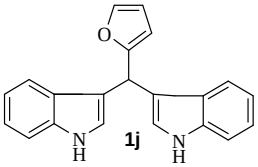
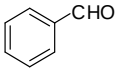
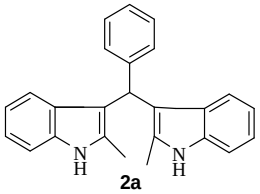
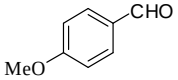
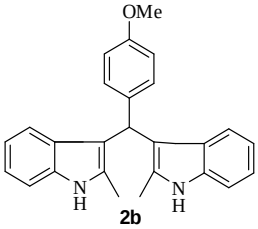
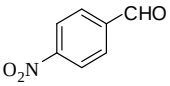
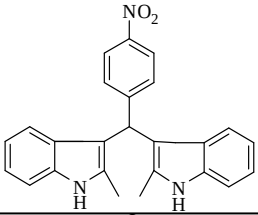
Scheme 1 Trichloroacetic acid catalyzed synthesis of bisindolylmethanes

Owing to versatile biological and pharmacological activities, synthesis of *bis*(indolyl) methane and its derivatives has received notable attention in these days as there is continuous flow of report for synthesizing these molecules in pursuit of novel, efficient synthetic methods and procedures. In recent years, we have witnessed numerous methods of the synthesis of *bis*(indolyl)methanes and its derivatives employing various protic as well as Lewis acids[21]. But Among all the methods reported so far, most of the existing methods involve use of toxic metal ions and solvents, longer reaction time, have high costs, use of corrosive reagents, tedious work-up procedures, lower product yields *etc*.. Consequently, newer ecofriendly and green synthetic methods are always in demand to surpass all these drawbacks.

Thus to, meet all these requirement with our continued long lasting interest in our lab to generate green, ecofriendly methods for the synthesis of novel heterocyclic compounds of biological importance, we applied solvent free technique for the synthesis of *bis*(indolyl) methanes utilizing trichloroacetic acid as a novel catalyst using grinding technique, which not only increases the rate of reaction but also offers product in quantative yield. Besides having use in organic transformations[22], Trichloroacetic acid possesses paramount importance in biochemistry, where it is routinely used during the precipitation of protein, DNA, RNA from tissue and other cell extracts at a normal concentration of 3-9% .Again it is also used as a herbicide, a weed killer, topically as an astringent, antiseptic, in cosmetic treatment like chemical peels, tattoo removal, treatment of warts including genital warts. Again as it kill normal cells due to which it is used uring pregnancy safely[23]. Thus due to these wide biochemical utility and literature survey enlightened us to use trichloroacetic acid as a catalyst, as there is no report on the synthesis of *bis*(indolyl) methanes under solvent free conditions, utilizing grinding technique at room temperature. Although one report where reductive alkylation of unsubstituted indoles with ketones can be achieved using trichloroacetic acid and triethylsilane[24], but it lack the formation of *bis*(indolyl)methane as the main product. While silica supported chloroacetic acid[25] has been utilized for this transformation, but owing to less toxicity profile trichloroacetic acid places itself superior in comparison to potentially dangerous monochloroacetic acid[26]. So in this present paper we have developed a new protocol for the efficient synthesis of *bis* (indolyl)methanes from the corresponding aromatic aldehydes and indoles via the electrophilic substitution of indoles with different aromatic aldehydes using trichloroacetic acid as a novel, ecofriendly, green catalyst utilizing grinding technique under solvent free reaction condition at room temperature.

Table 1 *Yield and reaction time of Trichloroacetic acid catalyzed various bis(indolyl)methanes*

Entry	X	Aromatic Aldehyde	Product	Time (min)	Yield %	M. P. (°C)
1.	H		 **1a**	5	89	96-98[27]
2.	H		 **1b**	5	91	76-78[27]
3.	H		 **1c**	5	92	222-224[27]
4.	H		 **1d**	5	87	121-123[27]
5.	H		 **1e**	5	88	108-110[28]
6.	H		 **1f**	5	88	178-181[29]
7.	H		 **1g**	5	90	110-112[27]

Entry	X	Aromatic Aldehyde	Product	Time (min)	Yield %	M. P. (°C)
8.	H		 **1h**	5	87	87-89[27]
9.	H		 **1i**	5	91	188-190[27]
10.	H		 **1j**	5	85	320-322[27]
11.	Me		 **2a**	5	87	246-248[30]
12.	Me		 **2b**	5	89	208-210[31]
13.	Me		 **2c**	5	92	240-242[30]

RESULT AND DISCUSSION

The electrophilic substitution of indole with aromatic aldehyde is catalyzed by trichloroacetic acid affording the product in excellent yield at room temperature. The reaction conditions on the reaction between indole and aldehydes are summarized in (Table 1).

Experimental Part

All the chemicals (AR grade) were purchased from SD fine chemicals and used without further purification. Melting points of the products were recorded using capillaries open at one end and were uncorrected. ^{1}H and ^{13}C NMR were recorded on 400 MHz Varian spectrophotometer in $CDCl_3$ solvent with TMS as an internal standard. IR was recorded on Bruker Vector 22 FTIR spectrophotometer using KBr discs. Exact mass of the samples were recorded on Shimadzu mass analyzer. The progress of the reaction was monitored by Thin Layer Chromatography in 20 % ethyl acetate: hexane.

Typical procedure bis(indolyl)methane synthesis

In a typical model condensation reaction trichloroacetic acid catalyst (10 mole %) was added to a mixture of aromatic aldehyde (10 mmol) and indole (20 mmol). At the moment the catalyst is added, the reaction starts instantly, with change in color from colorless to colored viscous mass and suddenly the reaction temperature rises by few degrees. Further the resulting mixture was ground fastly in the mortar using pestle for approximately five minutes. Further the reaction mass was kept as it is for 10 minutes to complete the reaction. After completion of the reaction as indicated by TLC (20 % ethyl acetate: hexane) the reaction mass was diluted with ethanol and after stirring for 5 minutes, the reaction mixture was poured onto the crushed ice. The seperated mass was washed several times with water and the pure product was obtained by recrystallization from ethyl acetate and petroleum ether. All the products reported are known compounds and were identified by comparison with physical and spectral data of authentic samples from literature. The spectral data of selected compounds is described below:

Compound (2b): Brown solid, m.p. 207-209 ^{o}C ,

(208-210) IR (KBr) cm^{-1} 3396, 3047, 2958, 2995, 1608, 1510, 1458, 1340, 1218, 1033; NMR (400 MHz $CDCl_3$) δ ppm 2.05(s, 6H), 3.8 (s, 3H), 5.95 (s, 1H), 6.8 (dd, 2H), 6.9 (dd,2H), 7.0 (m, 6H), 7.2(d, 2H), 7.73 (2H, br,s, NH); ESMS 409 (M^{+}); Elemental analysis Cal. C=82.07, H=6.36, N=7.36, found C= 81.9, H= 6.089, N=7.02.

Compound (2c): Yellow solid, m.p. 241-243^{o}C,

(**240-242**) IR (KBr) cm^{-1} 3385, 3056, 2913, 2844, 1618, 1593, 1515, 1461, 1424, 1385, 1341, 1223, 852; ^{1}H NMR (400 MHz $CDCl_3$) δ ppm 2.09(s, 6H), 6.059 (s, 1H), 6.85-6.92 (m, 4H), 7.05 (d, 2H), 7.25 (d, 2H), 7.4(d, 2H), 7.83 (s, 2H), 8.1 (s, 2H) ESMS 395 (M^{+}); Elemental analysis Cal. C=75.93, H= 5.35, N= 10.63; found C=73.77, H=5.31, N=10.64.

CONCLUSION

In summary, we have developed trichloroacetic acid catalyzed novel, solvent free, efficient environment benign method for the synthesis of pharmaceutically important *bis*(indolyl) methanes utilizing grinding technique at room temperature in excellent yield, which nicely places itself in the list of solvent free synthesis under grinding technique. This new protocol has striking features like cleaner reaction profiles, simple experimental and work-up procedures, high conversions, shorter reaction times to afford the products in excellent yield, hence believed to be superior over many existing synthetic methods of catalysts.

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